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Review

Current treatment of rectal cancer adapted to the individual patient

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ABSTRACT

Preoperative radiochemotherapy and total mesorectal excision surgery is a recommended standard therapy for patients with locally advanced rectal cancer. However, some subgroups of patients benefit more than others from this approach. In order to avoid long-term complications of radiation and chemotherapy, efforts are being made to subdivide T3N0 stage using advanced imaging techniques, and to analyze prognostic factors that help to define subgroup risk patients. Long-course radiochemotherapy has the potential of downsizing the tumor before surgery and may increase the chance of sphincter preservation in some patients. Short-course radiotherapy (SCRT), on the other hand, is a practical schedule that better suits patients with intermediated risk tumors, located far from the anal margin. SCRT is also increasingly being used among patients with disseminated disease, before resection of the rectal tumor. Improvements in radiation technique, such as keeping the irradiation target below S2/S3 junction, and the use of IMRT, can reduce the toxicity associated with radiation, specially long-term small bowel toxicity.

1. Background

Even though surgery has always been the historical backbone of rectal cancer treatment, since the first Northern American experiences of postoperative radiochemotherpy (RCT)[1] and Northern European experiences of preoperative exclusive radiotherapy,[2] it became evident that adjuvant treatment could be an effective way to obtain an outcome improvement.

Preoperative RCT and total mesorectal excision (TME) surgical procedure is a recommended standard therapy for patients with locally advanced rectal cancer (LARC), that is ≥T3 and/or ≥N1 disease. However, subgroup analyses in studies of preoperative treatment have not demonstrated a clinical benefit for patients whose tumors are confined to the bowel wall and who have negative lymph nodes. In the absence of significant survival advantages, it seems appropriate to focus our attention on defining benefits precisely and on selecting

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treatment options according to risk. Compelling reasons not to treat all patients with radiation, either preoperatively or postoperatively, include the risks of substantial toxic effects and long-term complications, specially the detrimental effects on bowel function.

The selection of a treatment modality depends on factors such as tumor histology, size, location, mobility, anatomic constraints, patient age, intercurrent medical disease and the technical expertise of the surgeon and radiation oncologist.

On the other hand, support is growing for the appealing concept of "wait and see" or even better "watch and wait" rather than proceed to radical surgery when a complete clinical response is observed. Hence, the management of patients who achieve a complete clinical response is becoming increasingly controversial.[3]

2. General principles of radiation therapy for rectal cancer

Radiotherapy is given to bulky primary tumor, positive nodes, and subclinical pelvic deposits. In resectable tumors, the main goal is to sterilize the surgical margins and the tissues at risk for subclinical disease outside them, or to increase sphincter saving rates by tumor downsizing in low laying tumors.

A dose between 45 Gy and 50 Gy at 2 Gy is considered adequate to control subclinical disease, thus, this is the dose needed to sterilize the surgical margins in patients with resectable tumors. In patients with unresectable tumors, the dose to control bulky tumors and to promote RO resectability must be higher, but this is strongly affected by the tolerance of pelvic organs.

It is known that biologically effective dose is related to the overall treatment duration and the fraction size. Short-course large daily fractionations (5 Gy/day, 5 days) should not be affected by repopulation. Biological effects of such a fractionation, according to the linear-quadratic model, are equivalent to 37.5 Gy in 2 Gy fractions.[4]

A prolonged interval before surgery, using preoperative long-course approach, could raise some concerns regarding the probability that metastases may develop in the meantime. Irradiation quickly reduces the number of viable tumor clonogens available for metastasis, thus, it seems reasonable to assume that preoperative RT eliminates the production of new micrometastases during treatment or in the interval between irradiation and surgery.

Concomitant chemotherapy can further reduce the occurrence of systemic metastases, but the exact contribution of chemotherapeutic agents to the final effect of treatment remains largely unknown. Better models to determine the mechanisms of radiosensitization and the therapeutic index of a treatment are needed.

No trial has ever shown that CRT or RT increase sphincter saving,[5,6] with the exception of the randomized Lyon R 96-2 trial which demonstrated not only sphincter preservation but organ (rectum) preservation after 10 years follow-up.[7,8]

3. Evidence of benefits in literature about preoperative radiotherapy: why adding a neoadjuvant treatment to surgery?

Surgical resection is the cornerstone of curative treatment for rectal cancer. Tumors in the upper and middle rectum can usually be managed with low anterior resection or coloanal anastomosis with preservation of the anal sphincter. For lower rectal tumors, with a distal edge of up to 6 cm from the anal verge, abdominoperineal resection (APR) has long been considered to be the standard operation. For patients with small rectal cancers that are confined to the rectal wall (T1 or T2), local excision techniques may offer local control rates that are comparable to APR, while preserving sphincter function, but this can not be considered a standard treatment for T2 rectal cancer. For patients with larger or more invasive tumors, neoadjuvant RCT has been utilized to promote tumor regression in an attempt to convert a planned APR into a sphincter-sparing surgical procedure.

The only definitive indication for neoadjuvant CRT, supported by results of randomized trials, is the presence of T3 or T4 rectal cancer. In 1997 the Swedish trial showed both a 5 year local control and survival improvement by adding preoperative RT (alone, with a short course – SCRT – schedule of fractionation), even if the group of patients underwent non standardized surgery.[9]

TME was developed after the recognition that discontinuous tumor deposits are often present in the lymphovascular tissue that surrounds the rectum (the mesorectum); left in place, such residual deposits are most likely the origin of local treatment failure. With the introduction of the TME, the local recurrence rates have dropped from 40 to 10 percent, approximately. Some physicians claim that adjuvant radiotherapy is not necessary if patients undergo resection with TME; however, it must be emphasized that TME series include patients with T1-2 N0 disease and allow identification and exclusion of patients with more advanced disease, compared with patients treated in the adjuvant trials in which more conventional surgery is performed. In the TME era, the Dutch trial obtained, for a population of T1–3 patients, a significant benefit for the arm adding short course radiation therapy (SCRT) to certified TME surgery (25 Gy in 5 fractions); this benefit remains at 6 year of median follow-up.[10]

Data from randomized trials suggest that the preoperative approach is associated with a more favorable long-term toxicity profile and fewer local recurrences than postoperative therapy The German study CAO/ARO/AIO-94 compared preoperative versus postoperative approach, delivering 45–50.4 Gy in 25–28 fractions with concomitant chemotherapy (CT).The two arms were similar apart from the administration of a boost of 5.4 Gy in the postoperative arm. Preoperative approach significantly decreased toxicity, and local recurrence, moreover, it increased sphincter preservation. The main outcomes remained at 11 years follow up.[11]

In the NSABP trial R-03, preoperative RCT was directly compared to postoperative RCT.[12] Preoperative RCT consisted of one cycle of bolus weekly 5-FU and leucovorin for six weeks, two courses of 5-FU and leucovorin (daily for five days during the first and fifth course of RT) concomitant with 50.4 Gy pelvic